Transplant center volume and outcomes in lung transplantation for cystic fibrosis

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Abstract: INTRODUCTION: Transplant volume represents lung transplant (LTx) expertise and predicts outcomes, so we sought to determine outcomes related to center volumes in CF. METHODS: United Network for Organ Sharing data were queried for CF patients receiving bilateral LTx from 2005-2015. Multivariable Cox regression was used to model survival to 1 year and long-term (>1 year) survival, conditional on surviving at least 1 year. RESULTS: 2,025 patients and 67 centers were included in the analysis. The median annual LTx volumes were 3 in CF (interquartile range [IQR]: 2, 6), and 17 in non-CF (IQR: 8, 33). Multivariable Cox regression in cases with complete data and surviving at least 1 year (n=1,510) demonstrated that greater annual CF LTx volume (HR per 10 LTx=0.66; 95% CI: 0.49, 0.89; p=0.006) but not greater non-CF LTx volume (HR=1.00; 95% CI: 0.96, 1.05; p=0.844) was associated with improved long-term survival in LTx recipients with CF. A Wald interaction test confirmed that CF LTx volume was more strongly associated with long-term outcomes than non-CF LTx volume (p=0.012). Center volume was not associated with 1-year survival. CONCLUSIONS: CF-specific expertise predicted improved long-term outcomes of LTx for CF, whereas general LTx expertise was unassociated with CF patients' survival.

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ABSTRACT

Introduction: Transplant volume represents lung transplant (LTx) expertise and predicts

outcomes, so we sought to determine outcomes related to center volumes in CF.

Methods: United Network for Organ Sharing data were queried for CF patients receiving bilateral LTx from 2005-2015. Multivariable Cox regression was used to model survival to 1 year and long-term (>1 year) survival, conditional on surviving at least 1 year.

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Conclusions: CF-specific expertise predicted improved long-term outcomes of LTx for CF, whereas general LTx expertise was unassociated with CF patients' survival.

INTRODUCTION

Lung transplantation (LTx) is a surgical treatment option for end-stage lung disease, including cystic fibrosis (CF).[1] Center volume of LTx has been used as a measure of center expertise, and has been shown to predict improved survival after this procedure.[2-4] High-volume centers are considered to attain better outcomes of LTx due to greater resource availability, more experience with complex care including extracorporeal membrane oxygenation (ECMO), and advanced understanding of transplant-related complications and therapeutic interventions.[2,5]

We have recently demonstrated that greater center volume of LTx was positively correlated with post-transplant survival specifically among patients diagnosed with CF.[6] However, a protective effect of increased center volume has paradoxical implications for LTx referral in this population. CF is the leading indication for LTx among children referred for this procedure,[7] therefore accounting for a large share of LTx performed at pediatric centers. These centers tend to have lower LTx volume than adult programs,[6] but may have greater expertise specific to performing LTx in CF patients. Using available registry data, we performed this study to determine whether center expertise in CF and non-CF LTx were equally associated with improved outcomes of LTx in CF.

METHODS

The local institutional review board approved analysis of de-identified transplant registry data with a waiver of individual consent. Data were obtained from the United Network for Organ Sharing (UNOS) registry,[8] which includes data on all solid organ transplant candidates and recipients in the United States (US). Patients were selected for analysis if they had been diagnosed with CF, received a first-time bilateral LTx between May 2005 and March 2015, and were age 12-50 years at transplantation. Forty-three patients age <12 years were excluded due to falling below the age cutoff for the lung allocation score [LAS] in the US. The robustness of the primary conclusions of the study to including patients age <12 years at transplantation is evaluated in the **Supporting Information**. During the period of May 2005 – March 2015, center volumes in each calendar year were calculated for LTx in CF patients (including patients not meeting criteria listed above), and LTx in all other patients. Centers were classified as adult if they had performed >50% of LTx in the overall period May 2005-March 2015 in patients age ≥18 years. The distributions of annual LTx volumes (CF and non-CF) were summarized across center-years using medians, ranges, interquartile ranges (IQR), and histograms.

Patient survival in days since LTx was analyzed using multivariable Cox proportional hazards regression. Outcomes included 1-year survival and, among patients surviving at least 1 year, long-term (>1 year) survival. The 1-year survival analysis included all patients. Potential confounders included in multivariable models were recipient and donor gender; recipient and donor age; recipient body mass index (BMI), LAS, serum creatinine, forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), supplemental oxygen requirement (L/min), preoperative extracorporeal membrane oxygenation (ECMO), most recent available 6-minute walk distance (6MWD), need for mechanical ventilation, time spent on the transplant waiting list, and the year LTx was performed. Cases with complete covariate data were included in multivariable analyses.

Cox proportional hazards models included continuous measures of center annual CF LTx and non-CF LTx volumes (number of transplants per year). Wald interaction tests were used to examine whether the coefficients for CF and non-CF LTx volume were equal. In each model, the proportional hazards assumption of Cox regression was evaluated using the Grambsch-Therneau global test. To assess whether the findings were confounded by differences in survival between pediatric and adult programs, the multivariable analysis was limited to the subsample of CF patients transplanted at adult centers. Data analysis was performed in Stata/IC 13.1 (College Station, TX: StataCorp LP) and two-sided $P<0.05$ were considered statistically significant.

RESULTS

There were 2,025 patients who met inclusion criteria, with patient characteristics summarized in **Table 1**. The cohort included 1,027 (51%) males and 998 (49%) females of mean age 28.7±8.8 years. There were 715 (35%) deaths during follow-up, of which 228 occurred during the first year post-transplant. Additionally, observations from 203 surviving patients were censored prior

to the first transplant anniversary. Cases in the analysis represented 67 transplant centers (60 adult, 7 pediatric) that contributed data over 526 center-years. Forty-five of the centers performed lung transplants (not limited to CF patients) as early as 2006 and as late as 2014 (i.e., the first and last full calendar years in the study period). Of the remaining 22 centers, 7 had performed a lung transplant in 2006 or earlier but ceased performing transplants by 2014-2015; while 15 performed no lung transplants during the study period prior to 2007. Over the 526 center-years, the median annual CF LTx volume was 3 (range: 1,22; IQR: 2, 6), while the median annual non-CF LTx volume was 17 (range: 0, 136; IQR: 8, 33). Histograms of annual CF and non-CF LTx volumes across center-years are presented in **Figures 1** and **2**, respectively.

After excluding patients missing data on covariates, multivariable Cox models were fitted to compare associations of annual CF LTx and non-CF LTx center volume with 1-year and long-term survival. In the multivariable models, annual center volumes were divided by 10, and select covariates were similarly re-scaled (where indicated by table footnotes) to enhance the interpretability of hazard ratios (HRs) and confidence intervals (CIs). As shown in **Table 2**, neither measure of center volume was associated with 1-year outcomes. Among patients surviving at least 1 year, however, the multivariable analysis of long-term survival in **Table 3** found that greater annual CF LTx volumes were associated with improved patient outcomes. Specifically, each 10 additional CF LTx performed at a particular center in a given year were correlated with 34% (95% CI: 11%, 51%; p=0.006) lower mortality hazard. By contrast, centerannual volume of LTx in non-CF patients was not associated with survival in this CF cohort (HR=1.00; 95% CI: 0.96, 1.05; p=0.844). A statistically significant Wald interaction test (p=0.012) was used to formally reject the null hypothesis that annual CF LTx volume and non-CF LTx volume had equally strong associations with post-transplant survival. A total of 6% of patients (127/2,025) were excluded from multivariate analysis due to missing data. There were

no statistically significant differences in center volume or survival outcomes between included and excluded patients, suggesting that this exclusion did not bias the multivariate analysis. The findings from this analysis were robust to including patients age <12 years at transplantation (**Supporting Information**).

Repeating this analysis in a subsample of CF patients transplanted at adult centers (**Table 4**), we confirmed that only annual CF LTx volume (HR=0.65; 95% CI: 0.47, 0.88; p=0.006) was associated with improved long-term survival, and that there was a statistically significant difference in the coefficients of annual CF and non-CF LTx volumes (Wald interaction test p=0.014). In both analyses of long-term survival (all patients surviving >1 year, and patients surviving >1 year who were transplanted in adult centers), global tests of the proportional hazards assumption were statistically non-significant (p=0.624 and p=0.466, respectively), suggesting that there was no variation of the center CF LTx volume effect over survival times past 1 year.

DISCUSSION

Recent studies have demonstrated that greater LTx volume is associated with improved patient survival, better management of complications, decreased need for re-admission, better outcomes for patients with risk factors such as ECMO support, and lower costs.[3-6,9] Although transplant volume is considered a valid measure of center expertise in LTx, these findings based on overall LTx volume should be interpreted cautiously when drawing implications for the population of LTx candidates with CF. In the US, patients with CF are disproportionately transplanted in pediatric and low-volume centers, so center expertise in LTx for CF may be discordant with their ranking according to total center LTx volume. In this study, we demonstrate that center annual CF LTx volume, and not annual volume of LTx in non-CF patients, is associated with improved survival among adolescents and adults with CF undergoing LTx.

Associations between greater transplant volume and improved patient outcomes are well-established across solid organ transplantation. For example, center-specific transplant volume is positively correlated with survival in lung, heart, and liver transplantation.[3-6,10-13] In the case of LTx, observed benefits of transplantation at a high-volume center have motivated recommendations to regionalize the practice of LTx,[12] refer patients with end-stage lung disease to high-volume LTx centers,[13] or transfer LTx candidates requiring ECMO support to high-volume centers.[2] Yet, evidence for the relevance of total center volume is tempered by some criticisms and limitations. First, center volume explains little of the variation in LTx outcomes.[3] Second, center volume may influence outcomes only among a subset of patients, such as patients requiring ECMO support.[2] Third, center volume may not capture all relevant aspects of center expertise, such as expertise with specific patient populations. Consistent with these insights, we have demonstrated that annual center volume of non-CF LTx (accounting for the majority of LTx performed)[1] was uncorrelated with survival of LTx recipients diagnosed with CF.

Meanwhile, center volume of CF LTx was associated with improved long-term post-transplant outcomes among CF patients, whether considering all CF LTx or specifically the CF LTx performed in adult transplant programs. Improved survival at high-volume centers has been attributed to greater resource availability and experience with more complex patients that may require emergent life support with ECMO, as well as an advanced understanding of transplant-related complications and optimal therapeutic interventions. In this study, we demonstrate that the association between center volume and long-term LTx outcomes appears to be conditional on the indication for LTx. Yet, it is unclear which specific practices of LTx programs experienced in CF improve outcomes for this specific patient population. These centers may have developed specific strategies in the following areas that are favorable to survival in CF LTx: donor and procurement techniques; perioperative management of the recipient; postoperative

management (including mechanical ventilation and hemodynamic strategies); fluid management; administration of medications (e.g., antimicrobials and immunosuppressants); and long-term management of nutrition, rehabilitation, infection, acute cellular and antibody-mediated rejection, chronic lung allograft dysfunction, and CF comorbidities. However, the lack of an association between CF LTx volume and early (1-year) outcomes suggests that expertise related to perioperative management or management of early LTx complications is unlikely to explain the survival advantage attributed to greater center volume in CF LTx.[6] Understanding changes in practice that develop as centers gain expertise in CF LTx may assist high-volume transplant centers without extensive expertise in CF when they perform LTx for this indication.

The current analysis confirms what has been previously reported in the CF population regarding older age being associated with improved survival post-LTx.[14] Recent analysis of the international CF population identified that with onset of the survival difference seems to occur at approximately 1 year post-transplant with an interesting caveat that this age-based survival disparity was particularly relevant when comparing children and adults transplanted at majority-adult programs in the US.[14] In other parts of the world, especially Europe and Australia, children with CF undergo LTx primarily at adult institutions where high overall transplant volume is combined with experience in pediatric CF patients, so the current study is reporting on the US experience. Since the inception of the LAS in the US, the adult CF population has experienced a significant survival benefit.[15] In comparison, the adolescent CF group has a higher hazard of post-LTx mortality that increases with attained rate with the highest risk being between 16 and 20 years of age but declines thereafter.[16] Although, we cannot identify the causality of this age disparity in post-LTx outcomes in CF, it clearly needs further study to improve survival in the younger CF population.

The central limitation of our analysis is the lack of data on mechanisms explaining how center CF LTx volume influences outcomes of CF patients undergoing LTx. Other limitations include the lack of important clinical variables relevant in CF. Specifically, data on bacterial or other infections were not collected; and some variables (e.g., pre-transplant FEV1 and FVC) had incomplete data. Additionally, we focused on the cohort of adolescent and adult patients with CF meeting the age cutoff (12 years) for donor lung allocation according to the LAS. Of this population, only 7% were transplanted in pediatric centers, so there exists a potential for referring CF LTx transplant candidates from adult to pediatric centers if the latter are more experienced in LTx specifically for CF. By contrast, among the 43 patients age <12 years at transplantation, 36 (84%) were already transplanted in pediatric centers, so the implications of the study for the youngest patients with CF requiring LTx are unclear. Despite these limitations, we have presented results that refine the role attributed to LTx center volume in outcomes of transplant recipients with CF. With our analysis limited to data from the US, future research should consider investigating center-volume influence on outcomes internationally. Nevertheless, our finding that only center volume specific to CF is associated with CF LTx recipients' long-term survival underscores the need to identify specific facets of center expertise that contribute to improved patient outcomes, and provides evidence against changing transplant policy or practice (e.g., referring patients to high-volume centers regardless of their indication for LTx) on the basis of center total procedural volume.

FIGURE CAPTIONS

Figure 1. Histogram of annual cystic fibrosis lung transplant volume (N=526 center-years).

Figure 2. Histogram of annual non-cystic fibrosis lung transplant volume (N=526 center-years).

DISCLAIMER

The data reported here have been supplied by the United Network for Organ Sharing as the contractor for the Organ Procurement and Transplantation Network. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the OPTN or the US Government.

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Table 1. Characteristics of cystic fibrosis patients undergoing lung transplantation.

Variable	Missing data	N (%)	Mean ± SD
Transplanted at pediatric center	0	144 (7%)	
Post-transplant mortality	0	715 (35%)	
Male recipient	0	1,027 (51%)	
Male donor	0	1,179 (58%)	
ECMO	0	83 (4%)	
Mechanical ventilation	0	218 (11%)	
Recipient age (years)	0		28.7 ± 8.8
Donor age (years)	0		30.6 ± 13.6
Year of transplant	0		2010 ± 3
Serum creatinine (mg/dL)	10		0.7 ± 0.3
Body mass index (kg/m^2)	2		19.4 ± 2.8
Final lung allocation score	1		47.2 ± 16.8
FEV_1 (% predicted)	69		25.0 ±13.4
FVC (% predicted)	45		39.0 ± 13.0
O_2 requirement (L/min)	30		4.8 ± 5.0
Days on waiting list	0		283 ± 496
6 minute walk distance (m)	36		270 ± 148

SD, standard deviation, ECMO, extracorporeal membrane oxygenation, FEV_1, forced expiratory volume in 1 second, FVC, forced vital capacity.

Table 2. Multivariable Cox proportional hazards models of 1-year patient survival after lung transplantation for cystic fibrosis (N=1,898).

Variable	HR	95% CI	P
Annual center LTx volume[a,b]			
CF	1.09	(0.73, 1.65)	0.666
Non-CF	0.98	(0.92, 1.04)	0.540
Male recipient	1.03	(0.76, 1.40)	0.860
Male donor	0.93	(0.69, 1.27)	0.656
ECMO	0.73	(0.31, 1.77)	0.491
Mechanical ventilation	1.41	(0.83, 2.40)	0.209
Recipient age (years)[a]	0.67	(0.55, 0.82)	<0.001
Donor age (years)[a]	1.11	(1.00, 1.23)	0.057
Year of transplant	0.96	(0.91, 1.01)	0.102
Serum creatinine (mg/dL)	1.73	(1.24, 2.43)	0.001
Body mass index (kg/m^2)	0.98	(0.93, 1.04)	0.512
Final lung allocation score	1.00	(0.88, 1.14)	0.999
FEV_1 (% predicted)[a]	0.85	(0.71, 1.01)	0.061
FVC (% predicted)[a]	1.03	(0.87, 1.20)	0.748
O_2 requirement (L/min)	1.02	(0.99, 1.06)	0.238
Days on waiting list[b]	1.02	(0.99, 1.04)	0.224
6 minute walk distance (m)[b]	0.89	(0.80, 0.99)	0.033

[a] Values divided by 10.
[b] Values divided by 100.

HR, hazard ratio, CI, confidence interval, LTx, lung transplant, CF, cystic fibrosis, ECMO, extracorporeal membrane oxygenation, FEV_1, forced expiratory volume in 1 second, FVC, forced vital capacity.

Table 3. Multivariable Cox proportional hazards models of long-term patient survival after lung transplantation for cystic fibrosis, among patients surviving at least 1 year (N=1,510).

Variable	HR	95% CI	P
Annual center LTx volume[a,b]			
CF	0.66	(0.49, 0.89)	0.006
Non-CF	1.00	(0.96, 1.05)	0.844
Male recipient	1.12	(0.91, 1.37)	0.277
Male donor	0.97	(0.79, 1.19)	0.765
ECMO	0.65	(0.25, 1.70)	0.383
Mechanical ventilation	1.54	(1.04, 2.28)	0.031
Recipient age (years)[a]	0.63	(0.56, 0.72)	<0.001
Donor age (years)[a]	1.01	(0.94, 1.08)	0.820
Year of transplant	1.07	(1.02, 1.12)	0.006
Serum creatinine (mg/dL)	1.12	(0.85, 1.49)	0.426
Body mass index (kg/m^2)	1.01	(0.97, 1.05)	0.587
Final lung allocation score	0.95	(0.87, 1.05)	0.324
FEV_1 (% predicted)[a]	1.01	(0.92, 1.11)	0.857
FVC (% predicted)[a]	0.97	(0.87, 1.07)	0.508
O_2 requirement (L/min)	1.00	(0.98, 1.03)	0.791
Days on waiting list[b]	0.98	(0.96, 1.00)	0.025
6 minute walk distance (m)[b]	0.97	(0.90, 1.04)	0.333

[a] Values divided by 10.
[b] Values divided by 100.

HR, hazard ratio, CI, confidence interval, LTx, lung transplant, CF, cystic fibrosis, ECMO, extracorporeal membrane oxygenation, FEV_1, forced expiratory volume in 1 second, FVC, forced vital capacity.

Table 4. Multivariable Cox proportional hazards models of long-term patient survival after lung transplantation for cystic fibrosis, among patients surviving at least 1 year who received lung transplant at majority-adult transplant centers (N=1,399).

Variable	HR	95% CI	P
Annual center LTx volume[a,b]			
CF	0.65	(0.47, 0.88)	0.006
Non-CF	0.99	(0.95, 1.04)	0.729
Male recipient	1.10	(0.89, 1.36)	0.391
Male donor	0.92	(0.74, 1.13)	0.428
ECMO	0.78	(0.30, 2.05)	0.613
Mechanical ventilation	1.57	(1.06, 2.34)	0.024
Recipient age (years)[a]	0.59	(0.52, 0.69)	<0.001
Donor age (years)[a]	1.00	(0.93, 1.08)	0.948
Year of transplant	1.08	(1.03, 1.13)	0.003
Serum creatinine (mg/dL)	1.10	(0.82, 1.48)	0.536
Body mass index (kg/m^2)	1.00	(0.96, 1.04)	0.991
Final lung allocation score	0.94	(0.85, 1.03)	0.190
FEV_1 (% predicted)[a]	1.01	(0.91, 1.11)	0.891
FVC (% predicted)[a]	0.95	(0.85, 1.05)	0.335
O_2 requirement (L/min)	1.00	(0.97, 1.03)	0.865
Days on waiting list[b]	0.98	(0.96, 1.00)	0.067
6 minute walk distance (m)[b]	0.95	(0.88, 1.02)	0.166

[a] Values divided by 10.
[b] Values divided by 100.

HR, hazard ratio, CI, confidence interval, LTx, lung transplant, CF, cystic fibrosis, ECMO, extracorporeal membrane oxygenation, FEV_1, forced expiratory volume in 1 second, FVC, forced vital capacity.